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(19) (CA) **CANADIAN PATENT** (12)

(54) Antimycotic Agents Which Have a Good Release of Active Compound and Are in the Form of Elastic Liquid Plasters

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"Antimycotic agents which have a good release of active compound and are in the form of elastic liquid plasters"

ABSTRACT OF THE DISCLOSURE

The inventnion relates to formulations of antimycotic active compounds, said formulations containg a spreading agent, a solubilising agent and a film-forming agent which is soluble in both water and organic solvents to provide high bioavailability of the active compounds and make short-term therapy possible.

The present invention relates to certain novel antimycotic formulations of antimycotic active compounds which may in themselves be known, which have a depot action, in spite of film formation, and a relatively high bioavailability of the active compounds and thereby make short-term therapy possible.

Formulations of antimycotic derivatives for the treatment of mycoses in humans, above all mycoses of the skin, have already been disclosed. Using these formulations, a therapy period of > 21 days has been required for a complete cure.

In order to shorten the period of therapy, a certain depot action and a relatively high bioavailability of the active compounds are required, in particular to eliminate the germs and in order to achieve a mycological cure. The known formulations are suitable for this only to a limited extent, because only a small proportion of the available active compound is released in the liquid volume at the site of infection. If a shortening of the period of therapy, for example to one day and a single application, is to be achieved without a further increase in the concentration of active compound, optimum bioavailability of the active compound must be ensured.

According to the present invention we provide a formulation which comprises an antimycotically effective amount of an antimycotic compound and inert pharmaceutical carrier containing a film-forming agent which is soluble or swellable both in water and in organic solvents, a spreading agent and a solubilising agent. In a preferred embodiment we provide an antimycotic formulation which comprises an antimycotically active compound,

2 to 10% of a spreading agent, 1 to 8% of a solubilising agent and, as a film-forming agent, a quick-drying polyvinylpyrrolidone, a terpolymer of 30% of vinylpyrrolidone, 40% of vinyl acetate and 30% of vinyl propionate, or a vinylpyrrolidone/vinyl acetate copolymer, which is soluble or swellable both in water and in organic solvents. The formulation can also contain any desired further formulation auxiliary or auxiliaries.

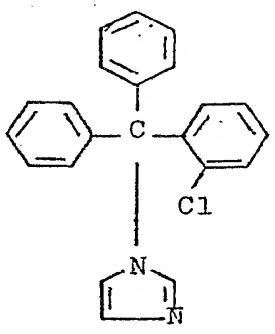
The formulations according to the present invention make possible optimum release of the active compound and hence a therapy period which is shortened to one day by high concentrations of the active compound being achieved. This effect is achieved by the presence of spreading-oils and solubilising agents and by the addition of adherent film-forming agents which allow the release of active compounds to be increased up to ten-fold and the action of the active compound thereby to be increased.

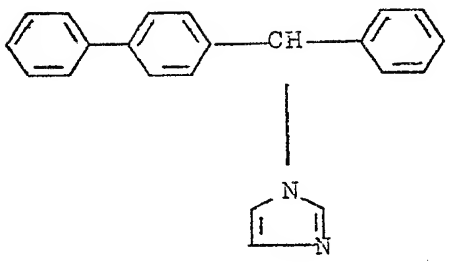
The formulations according to the invention, which are elastic liquid plaster formulations, represent a new application principle for dermal treatment of mycoses which, in addition to being very effective in applying the active compounds, provides, as a result of sealing the infection site, protection against infection of the surrounding area. The formulations according to the invention are particularly suitable for the treatment of nail mycoses.

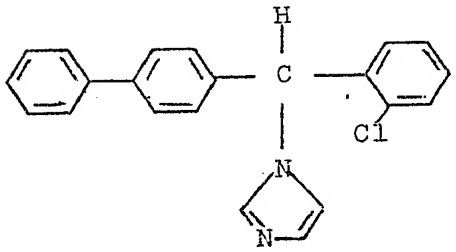
The formulations according to the invention can be either a solution or a spray.

Active compounds which can be formulated in this manner are any of the compounds having an antimycotic action, in particular imidazole derivatives and triazole derivatives. They are present in the agents according to the invention in amounts of 0.05 - 1%, preferably 0.1-1%. by weight.

The compounds with the following formulae may be mentioned as preferred examples:

(I)  clotrimazole,

(II)  trifonazole and

(III)  lombazole

Numerous ether azole derivatives having an antimycotic action are known from DE-OS (German Published Specification) 2,430,039. They can likewise be used as the active compound in the agents according to the invention.

By spreading agents there are understood oily liquids which are particularly readily distributed on the skin [R. Keymer, Parm. Ind. 32 (1970) 577 - 581]. The compounds which follow are particularly suitable as spreading agents for the agents according to the invention:

Silicone oils of various viscosities;

Fatty acid esters, such as ethyl stearate, di-n-butyl adipate, lauric acid hexyl ester, dipropylene glycol pelargonate, esters of a branched fatty acid of medium chain length with saturated C_{16}-C_{18}-fatty alcohols, isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}-C_{18} chain length isopropyl stearate, oleic acid oleyl ester, oleic acid decyl ester, ethyl oleate, lactic acid ethyl ester, waxy fatty acid esters, such as synthesised duck uropygial gland

fat, dibutyl phthalate, adipic acid diisopropyl ester and ester mixtures related to the latter;

Triglycerides, such as caprylic/capric acid triglyceride, triglyceride mixtures with vegetable fatty acids of C_8-C_{12} chain length or other specially selected naturally occurring fatty acids, partial glyceride mixtures of saturated or unsaturated fatty acids which optionally also contain hydroxyl groups and monoglycerides of C_8/C_{10}- fatty acids;

Fatty alcohols, such as isotridecyl alcohol, cetyl stearyl alcohol and oleyl alcohol; and

Fatty acids, such as, for example, oleic acid.

The compounds which follow are particularly suitable spreading-oils: isopropyl myristate, isopropyl palmitate, isopropyl stearate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}-C_{18} chain length, waxy fatty acid esters, such as synthesised duck uropygial gland fat, silicone oils, an isopropyl myristate/isopropyl palmitate/isopropyl stearate mixture and coconut oil acid isopropyl ester.

Preferred suitable solubilising agents for use in the formulations according to the present invention are benzyl alcohol, 2-octyl-dodecanol, polyethylene glycols, phthalates, adipates, propylene glycol, glycerol, dipropylene and tripropylene glycol and waxes and other additives used in cosmetics.

The gel-forming and film-forming agents are those macromolecular compounds, as defined previously, which can dissolve or start to swell both in water and in organic solvents and form a type of film after drying.

Suitable solvents are water and any of the water-miscible solvents. Possible solvents are, for example, alkanols (such as ethanol and isopropyl alcohol), propylene glycol, Methylcellosolve, Cellusolve, esters,

morpholines, dioxane, dimethylsulphoxide, dimethylformamide, tetrahydrofuran and cyclohexanone.

One or more solvents can be employed in the preparation of the formulations according to the invention.

The auxiliaries which follow can, inter alia, be used as appropriate in practice to establish an optimum formulation: glycerol, viscous paraffin, highly liquid paraffin, triethanolamine, collagen, allantoin, novantisolic acid and perfume oils.

Further auxiliaries which are suitable are:

(a) Substances which, for example, can stabilise a suspension, for example colloidal silicic acid or montmorillonites;

(b) Surface-active agents (including emulsifiers and wetting agents), for example

1. anionic surface-active agents, such as Na lauryl sulphate, fatty alcohol ether-sulphates and the monoethanolamine salts of mono-/di-alkyl polyglycol ether-orthophosphates;
2. cationic surface-active agents, such as cetyl trimethylammonium chloride;
3. ampholytic surface-active agents, such as di-Na-N-lauryl-β-iminodipropionate or lecithin; and
4. non-ionic surface-active agents, for example polyoxyethylated castor oil, polyoxyethylated sorbitane monocleate, sorbitane monostearate, cetyl alcohol, glycerol monostearate, polyoxyethylene stearate and alkylphenol polyglycol ethers;

(c) Stabilisers for preventing the chemical degradation which occurs in the case of some active compounds, such as antioxidants, for example tocopherols and butylhydroxyanisole; and

(d) Agueous solutions which have been rendered acid can be stabilised by the addition of preservatives which are

customary in cosmetics, for example p-hydroxybenzoic acid esters.

The following Examples illustrate formulations according to the present invention (in these Examples M.W. indicates the weight average molecular weight).

Example 1

Trifonazole	3.000	g
Benzyl alcohol	4.000	g
Isopropyl myristate	6.000	g
Vinylpyrrolidone/vinyl acetate copolymer	12.500	g
Isopropanol	to 100	ml

The individual components were mixed with one another at room temperature and thereby dissolved. The formulations of Examples 2 to 14 were prepared in the same way.

Example 2

Trifonazole	1.00	g
2-Octyldodencanol	2.00	g
Isopropyl myristate	6.00	g
Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
Isopropanol	to 100	ml

Example 3

Lombazole	1.00	g
Benzyl alcohol	5.00	g
Isopropyl stearate	6.00	g
Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
Isopropanol	to 100	ml

Example 4

Lombazole	0.10	g
Benzyl alcohol	6.00	g
Isopropyl myristate	6.00	g
Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
Isopropanol	to 100	ml

Example 5

Clotrimazole	1.00	g

	Benzyl alcohol	5.00	g
	Isopropyl myristate	6.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	12.50	g
	Isopropanol to	100	ml
	Example 6		
	Clotrimazole	1.00	g
	Benzyl alcohol	6.00	g
	Isopropyl myristate	6.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
	Isopropanol to	100	ml
	Example 7		
	Clotrimazole	1.00	g
	2-Octyldodecanol	2.00	g
	Isopropyl myristate	6.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
	Isopropanol to	100	ml
	Example 8		
	Clotrimazole	1.00	g
	Benzylalcohol	4.00	g
	Isopropyl myristate	6.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	12.50	g
	Isopropanol to	100	ml
	Example 9		
	Lombazole	1.00	g
	2-Octyldodecanol	8.00	g
	Isopropyl stearate/isopropyl myristate/ isopropyl palmitate	2.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
	Isopropanol to	100	ml
	Example 10		
	Lombazole	0.10	g
	2-Octyldodecanol	1.00	g
	Isopropyl myristate	10.00	g
	Vinylpyrrolidone/vinyl acetate copolymer	10.00	g
	Isopropanol to	100	ml

Example 11

Clotrimazole		1.0	g
Benzyl alcohol		5.0	g
Isopropyl myristate		6.0	g
Polyvinylpyrrolidone		12.5	g
Isopropanol	to	100	ml

Example 12

Lombazole		1.0	g
Benzyl alcohol		5.0	g
Isopropyl myristate/isopropyl palmitate/ isopropyl stearate mixture		6.0	g
Polyvinylpyrrolidone		12.5	g
Isopropanol	to	100	ml

Example 13

Clotrimazole		1.0	g
Benzyl alcohol		2.0	g
Isopropyl myristate		6.0	g
Terpolymer of 30% of vinylpyrrolidone, 40% of vinyl acetate and 30% of vinyl propionate		12.5	g
Isopropanol	to	100	ml

Example 14

Lombazole		1.0	g
Benzyl alcohol		5.0	g
Mixture of isopropyl myristate/isopropyl stearate and isopropyl palmitate		6.0	g
Terpolymer of 30% of vinylpyrrolidone, 40% of vinyl acetate and 30% of vinyl propionate		12.5	g
Isopropanol	to	100	ml

Example 15

Sprays

The active compound solutions prepared according to Examples 1 to 14 could also be processed to sprays. For this purpose, for example, 60 to 90% of active compound solution was mixed with 10 to 40% of a customary propellant, for example N_2, N_2O, CO_2, propane, butane or a halogenated hydrocarbon.

The following Example illustrates the activity of certain formulations according to the present invention.

Example A: Testing the activity of the agents according to the invention on Trichophyton-infected guineapigs.

Trichophyton-infected Pirbright white guineapigs with an average weight of 600 g were used as a test model for a comparative examination of the activity of the agents according to the invention. The backs of the animals were shaved with electric hair-clippers such that hair stubble about 1/10 mm long remained.

Infection with Trichophyton mentagrophytes was effected by lightly rubbing in a spore suspension of the pathogen, which had been initially germinated for 24 hours in Sabouraud nutrient solution, over an approximately 2 x 2 cm area of the shaved back of the animals. 0.5 ml of germ suspension, which contained 1 - 3 x 10^5 infectious fungus particles, were applied per animal.

In the case of this mode of infection, the first symptoms of dermatophytosis show as readdening and scaling of the skin 2-3 days after infection. In the case of untreated animals, the dermatophytosis is most pronounced about 14 days after infection: Loss of hair in patches and bloody integumentary defects within a phlogistically changed, scaly edge zone.

The formulations to be tested were applied locally once, on the 2nd day after infection, to the reddened infection sites on the animals. In each case 0.5 ml of the formulations (= 5 mg of active compound as 1% strength formulation) was applied. The course of the infection was evaluated daily up to the 20th day after infection.

The results are given in the following table (in which + = weak action, ++ = action, +++ = good action, ++++ = very good action).

Agent of Example	Action on Trichophyton-infected guineapigs
1	+++
2	++++
3	++++
4	++++
5	++++
6	++++
7	++++
8	++++
9	++++
10	+++
11	++++
12	++++
13	++++
14	++++

When formulations which contained water-insoluble polymers, for example methacrylates, instead of the polymers mentioned were used instead of the formulations according to the invention, the mycosis is aggravated.

When formulations which, in addition to the active compound, contained only the polymers mentioned and neither spreading agents nor solubilising agents were used, only a weak action is achieved.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A formulation which comprises an antimycotically effective amount of antimycotic compound and inert pharmaceutical carrier containing a film-forming agent which is soluble or swellable both in water and in organic solvents, a spreading agent and a solubilising agent.

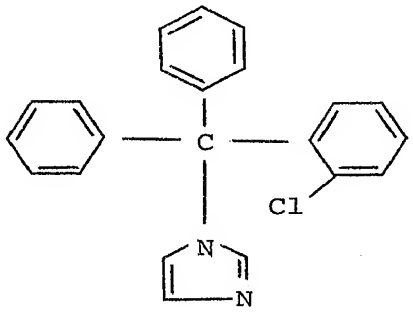
2. A formulation of claim 1, containing 2 to 10% of a spreading agent, 1 to 8% of a solubilising agent and, as a film-forming agent, polyvinylpyrrolidone, a terpolymer of 30% vinylpyrrolidone, 40% of vinyl acetate and 30% of vinyl propionate, or a vinylpyrrolidone/vinyl acetate copolymer, which is soluble or swellable both in water or in organic solvents.

3. A formulation according to claim 1 in which the anti-mycotic active compound is present in an amount of 0.05 to 1% by weight.

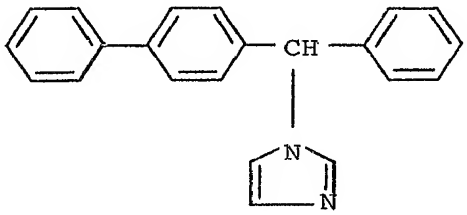
4. A formulation according to claim 1 in which the anti-mycotic is present in an amount of 0.1 to 1% by weight.

5. A formulation according to claim 1 or 2, in which the antimycotic active compound is an imidazole derivative or a triazole derivative.

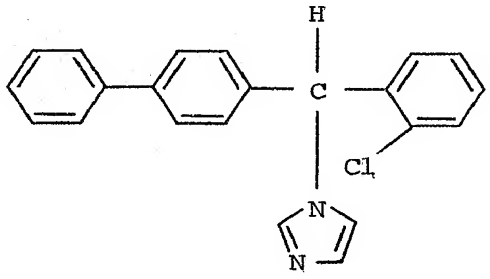
6. A formulation according to claim 1, 2 or 3, in which the antimycotic active compound is clotrimazole, of the formula



7. A formulation according to claim 1, 2 or 3, in which the antimycotic active compound is trifonazole, of the formula



8. A formulation according to claim 1, 2 or 3, in which the antimycotic active compound is lombazole, of the formula



9. A formulation according to claim 1 in the form of solution.

10. A formulation according to claim 1 in the form of a spray.

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PATENT AGENTS

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente